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Hypervitaminosis A

A Cause of Hypercalcemia

SUNITA C. BAXI, MD
GEORGE E. DAILEY III, MD
La Jolla, California

IN THE PRESENT CLIMATE of increased health and nutrition consciousness, physicians commonly see patients taking a host of different vitamin and mineral supplements, frequently in pharmacologic doses. One lipid soluble vitamin still available in large unit doses and in widespread use is vitamin A. Complications of hypervitaminosis A have been recognized for a number of years. However, hypervitaminosis A has been infrequently recognized as a cause of hypercalcemia. We wish to report the case of a patient who had pronounced hypercalcemia, rapidly reversible after discontinuation of large doses of vitamin A.

Report of a Case

A 29-year-old woman, a part-time employee of a health food store, presented with a four-week history of illness. She had consulted an ophthalmologist for dryness and irritation of her eyes, which prevented her from wearing contact lenses. She also noted redness and irritation of her gums and tongue, and fissures at the corners of her mouth (cheilosis). There was dryness and itching of her skin, as well as generalized weakness and malaise for approximately two weeks. Headache had begun one week before admission, it was occipital in location and moderately severe. She was forced to give up jogging because of muscle aches and pains, particularly in the anterior lower legs. Nausea, vomiting and pronounced weakness had been present for four to five days before her presentation.

Medications

On questioning, it was found that she had taken two tablets per day of a combination vitamin preparation, which contained 25,000 units of vitamin A and 100 units of vitamin D. She had taken two tablets per day for at least three months.

Thinking her dry eyes and mouth may be a manifestation of vitamin A deficiency, she took an additional 50,000 units of vitamin A a day for one week before presentation. She was taking no other medications. Specifically, there were no other sources of vitamin D, calcium supplementation or diuretics.

Physical Examination

The patient appeared moderately ill and weak. Height was 161 cm, weight 52.7 kg. Temperature was 37°C, pulse 52 and blood pressure 110/70 mm of mercury, with no orthostatic drop. There was cheilosis around the mouth and some erythema of the gums and mouth. There was no visible keratoconjunctivitis. The thyroid was normal in size. Findings on examination of the lungs, heart, breasts, abdomen and pelvis were within normal limits. The abdomen was soft. Liver span was approximately 8 cm. There was no palpable splenomegaly. The deep tendon reflexes were symmetrical and normal in timing.

Laboratory Data

The serum calcium concentration was reported to be notably elevated at 14.4 mg per dl. The serum phosphate level was 3.6 mg per dl. Other laboratory data included a leukocyte count of 4,500 with normal differential. Hemoglobin was 10.9 grams per dl. Hematocrit was 30.6 percent. Erythrocyte sedimentation rate was 43 mm per hour. Serum creatinine was 0.9 mg per dl. Pro-

From the Division of Diabetes and Endocrinology, Scripps Clinic and Research Foundation, La Jolla, California.

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Reprint requests to: George E. Dailey III, MD, Head, Division of Diabetes and Endocrinology, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Road, La Jolla, CA 92037.

thrombin time was 12.9 seconds with a control of 11.8 seconds. The serum sodium concentration was 142, potassium 3.9, chloride 112 and bicarbonate 24 mEq per liter. Serum aspartate aminotransferase (previously designated SGOT) was 101 and alanine aminotransferase (previously SGPT) was 50 IU per liter. Hepatitis-B surface antigen was negative. The 24-hour urinary calcium value was 454 mg. Creatinine clearance was 72 ml per minute. The thyroxine value was 4.8 μg per dl, thyroid stimulating hormone 4 μU per ml and triiodothyronine resin uptake 28.2 percent. The vitamin A level was 923 IU per dl (normal 65 to 275). The level three days after the patient stopped taking vitamin A had fallen to 610 IU per dl. The value for 25-hydroxy-vitamin D was 23 ng per ml (normal 10 to 55). An x-ray study of the chest and serum protein electrophoresis showed no abnormalities. Parathyroid hormone was appropriately suppressed at 10 μl equiv per ml (normal 10 to 80), with a concomitant serum calcium level of 15.2 mg per dl. No abnormalities were seen on x-ray films of the cervical spine, hands and tibia.

Hospital Course

The patient was treated with large doses of intravenously given saline for approximately 72 hours. The serum calcium concentration fell promptly (see Table 1). Symptoms of nausea, bone pain and headache disappeared rapidly in two to three days. Weakness and dry mouth persisted for approximately seven to ten days. Serum aspartate aminotransferase appeared to be falling after approximately ten days. Serum magnesium rose spontaneously upon resumption of regular diet. She was followed as an outpatient for two months after ingestion of vitamin A, and has remained normocalcemic.

Discussion

Hypervitaminosis A has been recognized as a potentially serious cause of illness for many years. The major side-effects include hepatocellular damage, which has led to fatal portal hypertension on occasion,[1,2] increased intracranial pressure, and gastrointestinal, cutaneous and musculoskeletal symptoms.[3] Hypercalcemia has been reported only rarely, and approximately seven patients have been described previously.[3-7] The minimum dose of vitamin A required to produce toxicity, particularly hypercalcemia, cannot be stated with certainty. The majority of patients have ingested 50,000 units per day or more for a prolonged period of time. The recommended daily allowance as established by the Food and Drug Administration at present is 5,000 IU per day. Nevertheless, despite its potential toxicity, vitamin preparations containing much larger amounts continue to be available without prescription.

Symptoms seen after ingestion of a single large dose of vitamin A are abdominal pain, nausea, vomiting, dizziness, sluggishness and irritability. Spontaneous recovery is usually seen.[3] In the early stages of chronic ingestion, vitamin A is stored in the liver and serum levels are low. When the storage capacity of the liver is exhausted, serum levels rise. Hypervitaminosis A causes symptoms referable to multiple organ systems. Of all the symptoms, hypercalcemia is reported rather infrequently.[3-7] In the published case reports, the range of hypercalcemia has been anywhere from 12 to 18.9 mg per dl. The calcium

TABLE 1.—*Change in Serum Calcium and Liver Enzymes After Stopping Vitamin A*

Date	Calcium (mg/dl)	Phosphate (mg/dl)	Parathyroid Hormone (μl equiv/ml)	Aspartate Aminotransferase (IU/liter)	Magnesium (mg/dl)	Vit. A (IU/dl)	Alanine Aminotransferase (IU/liter)	Urinary Calcium (mg/24 hr)	Creatinine Clearance (ml/min)
9/ 3/80	13.4	..	10*	...	..	...	..	...	..
9/ 5/80	14.4	..	..	...	..	923	..	...	..
9/ 6/80	11.3	..	..	...	..	...	..	...	..
9/ 7/80	10.2	..	..	...	..	...	..	...	..
9/ 8/80	10.8	3.6	..	103	0.8	610	50	454	80
9/ 9/80	10.0	..	..	...	..	...	..	...	..
9/10/80	11.0	..	..	111	1.4	...	62	...	..
9/11/80	11.0	..	..	...	..	...	..	...	..
9/12/80	11.1	..	..	...	..	...	..	...	..
9/16/80	10.1	..	..	85	..	...	44	...	..
10/13/80	8.4	..	..	...	..	...	..	...	..

Aspartate aminotransferase previously was designated SGOT and alanine aminotransferase was SGPT.

*Normal 10-80 μl equiv per ml.

level is reported to decrease within one day of hydration, and to reach normal ranges within ten days to a month. This was the case in our patient.

The mechanism of hypercalcemia in hypervitaminosis A remains unclear. Vitamin A probably acts directly on bone, causing stimulation of osteoclastic resorption or inhibition of osteoblastic formation, or both.[8] Fractures and modeling defects of long bones with increased bone resorption have been reported to occur in rats after a daily dose of 50,000 units of vitamin A for one week.[9] In tissue cultures, direct application of vitamin A acetate to mouse parietal bone caused focal bone resorption.[10] Characteristic periosteal calcifications have been reported in several patients with chronic ingestion. In our patient parathyroid hormone levels were suppressed as would be expected in a non-parathyroid hormone dependent form of hypercalcemia. In the case reported by Weiland and co-workers, the patient had normal parathyroid glands at surgery.[6]

Our patient had another manifestation of hypervitaminosis A: abnormal liver function. Hepatocellular damage, portal fibrosis and cirrhosis have been reported and are probably related to large deposits of vitamin A in the liver.[1,2,11] Liver biopsy studies have shown perisinusoidal fibrosis, central vein sclerosis and focal congestion associated with perisinusoidal lipid storage cells called Ito cells. Obliteration of Disse's spaces by Ito cells has been reported. Electron microscopy showed increase in basement membrane-like material and collagen within the perisinusoidal space in association with Ito cells.[2] These changes may obstruct hepatic blood flow, cause parenchymal cell atrophy and lead to portal hypertension.

Summary

In summary, we have reported a case of hypercalcemia resulting from hypervitaminosis A—an occurrence that has been reported infrequently. The hypercalcemia is easily treatable. Physicians should be aware of hypervitaminosis A causing hypercalcemia. In view of heightened public interest in vitamin A, hypervitaminosis A may become a greater problem in the future. All patients should be carefully questioned regarding vitamin and food supplements (information not usually included in medical histories). Considerable effort may be required to obtain this information. As has been emphasized previously, prohibition of direct marketing of doses of vitamin A in the pharmacologic amounts could help to decrease this potentially serious complication.[12] Additional public and physician education regarding potential toxicity of doses of vitamins far in excess of recommended daily allowances would help to reduce this public health hazard.

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Survival After Intracerebral Hemorrhage in Wegener's Granulomatosis

CHRISTOPHER BAILLIE HEARNE, MD
Salt Lake City

EDWARD T. ZAWADA, Jr, MD
Richmond, Virginia

WEGENER'S GRANULOMATOSIS has been well known since its original description in 1936[1] as a necrotizing granulomatous vasculitis involving upper and lower respiratory tracts as well as the kidneys. Since that time the systemic nature of the illness with involvement of virtually all organ systems has been stressed.[2] Drachman first emphasized the neurologic complications of the ill-

From the Department of Medicine, University of Utah, and the Veterans Administration Medical Center, Salt Lake City. Dr. Zawada is now affiliated with the Department of Medicine, Medical College of Virginia, and the Veterans Administration Medical Center, Richmond, Virginia.

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Reprint requests to: Edward T. Zawada, Jr., MD, Assistant Chief, Medical Service (111), McGuire VA Medical Center, Richmond, VA 23249.